Cardiovascular Risks Comparable with Two Pain Killers, Etoricoxib and Diclofenac

Speaker: Christopher P. Cannon, MD, Associate Professor of Medicine, Harvard Medical School, and Associate Physician, Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts

Results from a late-breaking clinical trial showed that etoricoxib (Arcoxia, Merck), a highly selective cyclooxygenase-2 (COX-2) inhibitor, and the pain medication diclofenac (Voltaren, Novartis), a COX-1/COX-2 inhibitor, both of which are nonsteroidal anti-inflammatory drugs (NSAIDs), carried comparable rates of thrombotic cardiovascular events. Selective COX-2 inhibitors, such as rofecoxib (Vioxx, Merck) have previously been implicated in increasing the risk of heart attack and stroke. More recently, evidence suggests that most NSAIDs, whether selective COX-2 inhibitors or not, may also increase cardiovascular risk.

To assess the difference in cardiac risk between these two types of pain agents, investigators conducted the Multinational Etoricoxib and Diclofenac Arthritis Long-term study program (MEDAL). This is the largest randomized trial ever performed for arthritis. The trial enrolled 34,701 osteoarthritis and rheumatoid arthritis patients from 38 countries, including the U.S. Because all of the patients in the study had debilitating arthritis, there was no placebo group.

The patients, who were older than 50 years of age, had reasons to be using NSAIDs. They were randomly assigned to receive either etoricoxib 60 mg or 90 mg twice daily or diclofenac 150 mg once daily. The patients were followed for up to three years for an average of 18 months.

The primary endpoint was the rate of any thrombotic cardiovascular event. Overall, there was no hint of any difference in the risk of cardiac events, heart attack, or stroke. There were 1.24 events per 100 years for patients receiving etoricoxib and 1.30 events per 100 years for those taking diclofenac.

Patients in both groups experienced equal pain relief. The rates of complicated upper gastrointestinal (GI) events leading to perforation or obstruction were also virtually the same with both drugs, one event per 300 patient-years. The rate of uncomplicated ulcers, however, was lower with etoricoxib, for an overall rate of upper GI events of about two events per 300 patient-years, compared with three events per 300 patient-years for diclofenac.

Patients receiving high-dose etoricoxib discontinued the study agent more frequently than those receiving the lower dose because of edema. Both doses of etoricoxib were associated with higher rates of discontinuation of therapy as a result of hypertension.

Pioglitazone and Management of Cardiovascular Risk in Diabetic Patients

Speaker: Theodore Mazzone, MD, Professor of Medicine and Pharmacology, and Chief of the Section of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Illinois, Chicago

Pioglitazone (Actos, Takeda), a diabetes medication that improves sensitivity to insulin, appears to stop the progression...
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Carperitide and Nicorandil Promising in Acute Myocardial Infarction

Speaker: Mosafumi Kitakaze, MD, PhD, Director of the Cardiovascular Division, National Cardiovascular Center, Suita, Japan

Results from the Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage by Atrial Natriuretic Peptide (ANP) or Nicorandil (J-WIND) trial indicate that human atrial natriuretic peptide (carperitide) (Daichi Suntory/Astellas) significantly reduced infarct size and increased left ventricular (LV) ejection fraction in patients with acute ST-segment elevation myocardial infarction (MI), compared with no difference with nicorandil (Icorel, Sanofi-Aventis) and placebo in the two co-primary endpoints.

The prospective, placebo-controlled J-WIND study encompassed 1,216 patients with acute MI at 65 medical centers in Japan. Patients were randomly assigned to receive carperitide, nicorandil, or placebo. The carperitide patients received the drug as an infusion of 0.025 mcg/kg for three days. Patients in the nicorandil group received an initial dose of the bolus, followed by an infusion of 1.67 mcg/kg per minute for 24 hours.

The primary endpoint of infarct size was 14.7% lower with carperitide than with placebo, but there was no difference between nicorandil patients and controls. The co-primary endpoint of LV ejection fraction was increased by 5.1% with carperitide, compared with placebo, but treatment with nicorandil and placebo showed no difference.

Fondaparinux Reduces Mortality and Re-infarction in Non-reperfused STEMI Patients

Speaker: Lars C. Wallentin, MD, PhD, Professor of Cardiology, Uppsala Clinical Research Centre, Uppsala, Sweden

In non-reperfused patients with acute ST-segment elevation myocardial infarction (STEMI), fondaparinux (Arixtra, GlaxoSmithKline), an anticoagulant that inhibits activated Factor X, reduced mortality and re-infarction without increasing bleeding or stroke when it was administered for eight days, compared with unfractionated heparin (UFH) for 48 hours or placebo.

Approximately 30% of patients with STEMI do not receive fibrinolytic therapy. An analysis was designed to evaluate the effect of fondaparinux 2.5 mg once daily for up to eight days in 2,864 patients who did not receive reperfusion therapy in the Organization for the Assessment of Strategies for Ischemic Syndromes-6 (OASIS-6) trial.

The original trial was a randomized, double-blind comparison of fondaparinux 2.5 mg once daily versus placebo if UFH was not indicated or versus UFH for up to 48 hours, followed by placebo for up to eight days if UFH was indicated. The trial included 12,092 patients with STEMI from 447 hospitals in 41 countries; patients were followed for 180 days, from September 2003 to January 2006.

At 30 days, mortality and re-infarction rates were reduced from 15.1% in the controls (212 of 1,409 patients) to 12.2% in the fondaparinux patients (178 of 1,458 patients) (P = .027). These
beneﬁts were observed at nine days and at the study’s end at 180 days. There was no signiﬁcant difference in the incidence of stroke or major bleeding. At 30 days, the composite outcome of death, re-infarction, or severe bleeding, however, was signiﬁcantly reduced with fondaparinux (15.3% vs. 12.6% for controls; \( P = .037 \)). At the end of the study, the composite outcome was signiﬁcantly reduced by 20.5% with treatment and by 17% in the control group (\( P = .023 \)).

Valsartan and Prevention of New-Onset Atrial Fibrillation in Hypertension

Speaker: Roland E. Schmieder, MD, Professor of Medicine, Medizinische Klinik 4, Nephrology and Hypertension, University Erlangen Nürnberg, Erlangen, Germany

Valsartan (Diovan, Novartis)-based antihypertensive therapy was more effective in preventing new-onset atrial ﬁbrillation (AF) in hypertensive patients than amlodipine (Norvasc, Pfizer)-based therapy.

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial enrolled 15,245 patients at high cardiovascular risk. This prospective, double-blind, active-controlled study was conducted at 934 clinical sites in 31 countries. Patients were randomly assigned to take either valsartan 80 to 160 mg/day or amlodipine 5 to 10 mg/day, combined with additional antihypertensive agents (e.g., diuretics, beta blockers, and others) for an inﬁnite period of time (as of this date, up to four years).

The original study’s ﬁndings suggested no statistically signiﬁcant disparity between the two treatment groups in the primary endpoint of cardiac mortality and morbidity rates (10.6% for valsartan; 10.4% for amlodipine), despite unintended differences in blood pressure (especially early in the trial) that favored the amlodipine-based therapy.

Because AF increases cardiovascular risk in patients with hypertension, an analysis of the data was performed according to a secondary prespeciﬁed objective to compare the effect of both treatments on new-onset AF. Electrocardiography (ECG) recordings were obtained every year and were analyzed at a central laboratory for left ventricular (LV) hypertrophy and new-onset AF.

At the initial baseline evaluation, AF was diagnosed in 2.6% of the valsartan patients and in 2.6% of the amlodipine patients. During antihypertensive treatment, the incidence of at least one documented occurrence of new-onset AF was 3.6% in the valsartan patients and 4.3% in the amlodipine patients (odds ratio, 0.84; \( P = .044 \)). For the next four years, the corresponding odds ratios were as follows:

- 0.690 (\( P = 0.035 \)) in the ﬁrst year
- 0.694 (\( P = .0108 \)) in the second year
- 0.708 (\( P = .011 \)) in the third year
- 0.832 (\( P = .120 \)) in the fourth year

The incidence of persistent AF was 1.35% for valsartan and 1.97% for amlodipine (odds ratio, 0.681; \( P = .005 \)). Taking potentially confounding factors such as age, a history of coronary artery disease, and LV hypertrophy into account, the incidence of AF remained signiﬁcant (higher with amlodipine than with valsartan) for at least one case of AF and for persistent AF.

Clopidogrel Plus Aspirin Beneﬁts Patients at Higher Risk for Cardiovascular Disease

Speaker: Keith A. Fox, MD, Professor of Cardiology, and Head of Medical and Radiological Services, Department of Cardiological Research, University of Edinburgh, Edinburgh, United Kingdom

The impact of risk status, prior history, and proximity to recent cardiovascular events such as a myocardial infarction (MI) or stroke plays a major role in the efﬁcacy of clopidogrel (Plavix, Sanofi-Aventis) when added to aspirin therapy in patients with symptomatic coronary artery disease, cardiovascular disease, peripheral artery disease, or a history of cardiovascular (CV) events.

In the CHARISMA study (Clopidogrel for High Atherosclerosis Risk and Ischemic Stabilization, Management, and Avoidance), 15,603 patients were treated with aspirin. They were then randomly assigned to receive clopidogrel or placebo over a median of 28 months. The primary endpoint was cardiovascular death, MI, or stroke.

The initial results showed a nonsigniﬁcant trend favoring clopidogrel in 6.8% of treated patients, compared with 7.3% of placebo patients. The data were then further analyzed to see whether patients’ risk status at baseline and their proximity to a resulting CV event inﬂuenced their response to long-term dual antiplatelet therapy.

The incidence of CV death, MI, and stroke was 7% with clopidogrel patients and 7.8% with placebo. These ﬁndings were consistent with those of the trial’s primary endpoint.

When CV outcomes were assessed according to quartiles of baseline CV risk, only in the quartile with the greatest CV risk did a strong trend exist for a reduced risk of CV events with the addition of clopidogrel to aspirin.

When clopidogrel treatment was begun within six months after a stroke or MI, the beneﬁt of clopidogrel therapy had a signiﬁcant effect on the rate of future death, MI, or stroke. In patients with a documented prior vascular event or with conﬁrmed peripheral arterial disease, the risk of death, MI, or stroke was 7.3% with clopidogrel therapy versus 8.8% with placebo.

Effects of Bivalirudin in Elderly Patients with Non–STE Acute Coronary Syndrome

Speaker: E. Magnus Ohman, MD, Professor of Medicine, and Director of the Program for Advanced Coronary Disease Cardiac Catheterization and Angioplasty, Duke University Medical Center, Durham, North Carolina

Elderly patients (65 years of age and older) with non–ST-segment elevation acute coronary syndrome (NSTE–ACS) had similar outcomes for ischemia, lower rates of non-coronary artery bypass graft (CABG) surgery and bleeding, and similar clinical outcomes at 30 days with bivalirudin (Angiomax, The Medicines Company), compared with glycoprotein IIb/IIIa inhibitors (GPI) plus heparin or low-molecular-weight
A post hoc analysis of two phase 3 efficacy trials was performed:

- the EURopean In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS)
- the American–Australian–African trial with DronedarOne In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS)

The analysis was undertaken to evaluate the efficacy of dronedarone in reducing recurrences of AF in patients who had taken at least one antiarrhythmic agent before randomization and who had discontinued the study because of the lack of that agent's efficacy.

In the EURIDIS and ADONIS trials, 1,237 patients were randomly assigned, in a 2:1 fashion, to receive either dronedarone 400 mg twice daily (n = 828) or placebo (n = 409) in an outpatient setting. The patients were followed for 12 months.

The primary endpoints in both studies were the times to the first documented AF recurrences, as detected by electrocardiography (ECG) or trans-telephonic ECG monitoring. A Cox regression model was used to determine the efficacy of dronedarone in patients whose previous treatment with class 1A, 1C, or III antiarrhythmic agents or sotalol (Betapace, Berlex) had failed.

Overall, dronedarone lowered the risk of a first recurrence of AF by 25% (P = .0001), compared with placebo. For the primary endpoints of the two studies, the median time to first AF recurrence was 116 days with dronedarone and 53 days with placebo.

Dronedarone showed superior efficacy to placebo in all four subgroups (class 1A, class 1C, class III, and sotalol). Adverse events in each subgroup were in line with the consistently favorable overall EURIDIS and ADONIS trial results.

Torcetrapib/atorvastatin, a novel investigational drug combination, produced substantial elevations in high-density lipoprotein-cholesterol (HDL-C) and marked reductions in low-density lipoprotein cholesterol (LDL-C), compared with atorvastatin (Lipitor, Pfizer) alone in patients with heterozygous familial hypercholesterolemia (HeFH). Torcetrapib, a cholesterol ester transfer protein inhibitor, raises HDL-C levels. Atorvastatin, a statin drug, significantly reduces LDL-C levels.

A phase 3 clinical study was designed to assess the lipid
efficacy of the combination versus atorvastatin alone. In this multicenter, double-blind trial, 437 patients received atorvastatin 20 mg, 40 mg, or 80 mg daily for 4 to 16 weeks. Doses were titrated to attain an LDL-C level according to National Cholesterol Education Panel Adult Treatment Panel III (NCEP ATP III) criteria or the maximum tolerated dose.

Patients were then randomly assigned to receive 24 weeks of treatment with torcetrapib/atorvastatin or atorvastatin alone; they received either torcetrapib 60 mg, combined with atorvastatin at the dose reached at the end of the titration period, or atorvastatin alone, at the dose reached at the end of the titration period.

The combination regimen raised mean HDL-C levels by 57.7% from baseline while lowering LDL-C levels by 18.3%, compared with a 1% increase in HDL-C and an increase in LDL-C levels of 8.75% for atorvastatin alone.

Drug-related discontinuation rates attributable to adverse events were 6.3% for torcetrapib/atorvastatin and 2.8% for atorvastatin alone. There was no sign of increased rates of liver enzyme elevations or muscle-related adverse events.

Compared with atorvastatin alone, torcetrapib/atorvastatin did show an average increase of 2.01 mm Hg from baseline in systolic blood pressure.

*Editor’s Note:* On December 2, 2006, Pfizer decided to suspend all clinical trials with torcetrapib/atorvastatin because of an increased mortality rate among the subjects receiving the combination, compared with those receiving atorvastatin alone.